



NOTES

ANAEROBIC RODS

MICROBE OVERVIEW

- Rod-shaped (bacilli) bacteria, gram-positive, strict anaerobes

ANAEROBIC RODS SUMMARY

SPECIES	HOST	TRANSMISSION	PATHOLOGY
CLOSTRIDIUM BOTULINUM	Humans, animals	Ingestion/wound contamination	Botulism
CLOSTRIDIUM DIFFICILE	Humans, animals	Direct fecal-oral route	Pseudomembranous colitis, toxic megacolon
CLOSTRIDIUM PERFRINGENS	Humans, animals	Contamination of wounds, ingestion	Gas gangrene, food poisoning
CLOSTRIDIUM TETANI	Humans, animals	Contamination through wounds	Tetanus

CLOSTRIDIUM BOTULINUM (BOTULISM)

osms.it/clostridium-botulinum

PATHOLOGY & CAUSES

- Ubiquitous presence (esp. soil, water); **spore-forming**; catalase negative, superoxide dismutase positive, subterminal endospore
- Fermentation
 - Carbohydrates
- Obligate anaerobe, can tolerate small amounts of oxygen due to superoxide

dismutase

- Potential bioterrorism weapon
- Absorption of toxin into bloodstream → spreads to nervous system → binds to presynaptic receptors → endocytosis → cleavage of SNAP-25 protein → **lack of acetylcholine** with impaired transduction

Virulence factors

- Seven distinct types of neurotoxins (A–G)
 - **Type A**: most potent

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- Heat-resistant
 - Toxins enduring temperature of 100°C/212°F for several hours
- H-antigen from flagelle

Culture

- Chopped meat, glucose, starch medium for isolation; egg yolk agar incubation in anaerobic conditions

Disease

- Causes disease characterized by muscle weakness, nervous system impairment
- Infant botulism
 - Spores ingestion → germination in gastrointestinal (GI) tract → toxin produced *in vivo*
- Foodborne
 - Ingestion of botulinum toxin-contaminated food
 - Average incubation period is 12–36 hours
- Wound botulism
 - Wound infection with spores → toxin produced *in vivo*
 - Average incubation period is 10 days
- Adult intestinal toxemia botulism
 - Colonization of intestines with toxins production
- Iatrogenic botulism
 - Complication of therapeutic use of botulinum neurotoxins
- Enteric infectious botulism
 - *C. botulinum* colonizes adult GI tract

RISK FACTORS

- Infant botulism
 - Honey consumption in first year of life; ingestion of dust/soil containing *C. botulinum* spores
- Foodborne botulism
 - Home-canned, improperly preserved food; smoked fish
- Wound botulism
 - IV/subcutaneous drug usage; crush injuries
- Enteric infectious botulism
 - Achlorhydria/other GI diseases → colonization

COMPLICATIONS

- Sudden infant death syndrome (SIDS), seizures, ileus, death

SIGNS & SYMPTOMS

- General symptoms precede muscle weakness
 - Abdominal pain, nausea, vomiting, lack of fever (wound botulism only type with fever)
- Cranial nerve impairment
 - Dilated pupil, ptosis; double vision (due to disconjugate eye movement); ophthalmoplegia; dry mouth, difficulty swallowing; loss of facial expressions
- Progressive symmetrical muscle weakness descending from head
 - Hypotonia, hyporeflexia; floppiness in infants
 - Respiratory muscles: breathing difficulties
- Hyperactivation of autonomic system
 - ↓ salivation, lacrimation, orthostatic hypotension, obstipation, urine retention

DIAGNOSIS

LAB RESULTS

- Toxin detection/bacteria isolation

Enzyme-linked immunosorbent assay (ELISA), mass spectroscopy, polymerase chain reaction (PCR)

- Isolation of *C. botulinum* from feces, vomitus, food

OTHER DIAGNOSTICS

- History, physical examination

Electromyogram (EMG)

- Short-lasting motor unit potentials with small amplitude

TREATMENT

MEDICATIONS

- IV botulinum immunoglobulin/heptavalent botulinum antitoxin
 - Manage infection
- Antibiotics
 - Manage secondary infection
- Cholinesterase inhibitors

OTHER INTERVENTIONS

- Manage infection
 - Debridement, irrigation of wound
 - Colon cleansing (enema, cathartics)
- Nasogastric tube (feeding), Foley catheter (urinary retention), intubation/mechanical ventilation

Prevention

- Pentavalent-botulinum-toxoid (PBT) vaccine
 - Five dose vaccination with booster dose once per year

CLOSTRIDIUM DIFFICILE (PSEUDOMEMBRANOUS COLITIS)

osms.it/clostridium-difficile

PATHOLOGY & CAUSES

- Ubiquitously present, can be part of “normal” flora; subterminal endospore; motile
- Intestinal microbiota disturbance → infection, colonization of gut → produces A, B toxins → binds to receptors on intestinal wall → internalization → fusion with lysosome → toxins exit endosome → damage of cytoskeleton → cell apoptosis → inflammatory response with accumulation of inflammatory cells, fibrin, dead cells → formation of membrane-like structure (pseudomembrane)

Virulence factors

- Enterotoxin A (TcdA), cytotoxin B (TcdB), H-antigen from flagelle

Culture

- Agar with cycloserine, cefoxitin, fructose
- *C. difficile*-associated colitis combined with formation of pseudomembranous plaques

Transmission

- Fecal-oral route by ingestion of spores

RISK FACTORS

- Antibiotic exposure
 - Disturbance of intestinal microbiota
- Previous hospitalization
 - ↑ risk for infection
- Children with neutropenia
 - More prone to common bacterial infections requiring antibiotics → disturbance of intestinal microbiota
- Gastric acid suppression, > 65 years, comorbidities

COMPLICATIONS

- Multiple relapses, dehydration (due to excessive diarrhea)

GI complications

- Toxic megacolon (due to inflammation damaging muscularis propria, underlying neurons); ileus; colon perforation; intussusception; pneumatosis; ascites; sepsis

Extraintestinal complications

- Splenic abscess; osteomyelitis

SIGNS & SYMPTOMS

- Watery diarrhea (most common) with mucus/blood
- Abdominal distension, cramps
- Malaise
- Fever

DIAGNOSIS

DIAGNOSTIC IMAGING

Sigmoidoscopy/colonoscopy

- Visualization of plaques

LAB RESULTS

WBCs

- ↑ white blood cells

Stool analysis

- Presence of blood/mucus
- Stool culture
- Enzyme immunoassay test
 - Detection of glutamate dehydrogenase antigen
- Toxin detection
 - Enzyme immunoassay, real-time PCR
- Cell culture cytotoxicity assay
- Biomarkers
 - Differentiation between colonization, actual disease; ↑ fecal cytokines, CXCL5, phosphorylated p38

TREATMENT

MEDICATIONS

- Mild disease: oral metronidazole
- Severe disease: oral vancomycin
- Complications: combination of oral vancomycin, IV metronidazole
- Second relapse: oral vancomycin tapered
- Recurrent: probiotics

SURGERY

- Colectomy
 - In persons with acute abdomen, refractory colitis, fulminant colitis

OTHER INTERVENTIONS

- End previous antibiotic use
- Second relapse: pulse therapy
- Recurrent: biological therapies
 - Fecal microbiota transplant: transplantation of microbiota from healthy individual
- Electrolytes, fluids replacement; appropriate nutrition
- Prevention of hospital-acquired infection
 - Infection control protocol, antibiotic stewardship

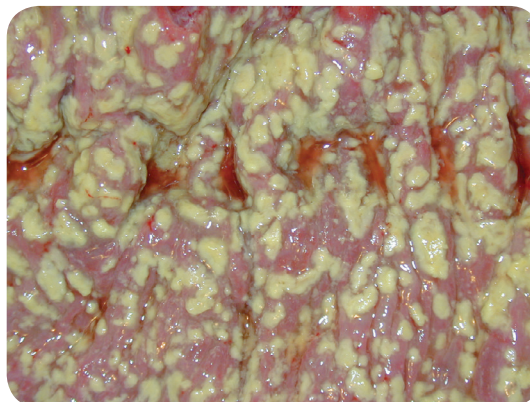


Figure 56.1 The gross pathological appearance of the colonic mucosa in pseudomembranous colitis.

CLOSTRIDIUM PERFRINGENS

osms.it/clostridium-perfringens

PATHOLOGY & CAUSES

- Ubiquitous in nature, also part of human microbiota; subterminal **endospore**; nonmotile

Virulence factors

- Divided into subtypes A–E
- Produces 12 toxins
- **Alpha**
 - Enzyme **lecithinase** splits **lecithin** → ↑ vascular permeability → **cell destruction**
 - **Responsible for gas gangrene, hemolysis**
- **Beta**
 - Formation of selective pores → ↑ permeability with cell destruction
 - **Responsible for enteritis necroticans**; deactivated by trypsin
- **Epsilon**
 - Pores form on cells → destruction
- **Iota**
 - **AB toxin**: enzyme (A), binding (B) domain
 - Destruction of cells through affection of cytoskeleton

Culture

- Growth on tryptose sulfite cycloserine agar

Clostridial gas gangrene

- Saprophytic anaerobic bacteria → clostridial gas gangrene due to tissue infection/food poisoning through ingestion
- Disease characterized by necrosis, gangrene due to infection of skin, deep tissues
- Bacteria produces gas → characteristic crepitation sound during palpitation
- Divided into
 - **Traumatic**: wound → spore inoculation → bacteria growth in appropriate anaerobic conditions → production of toxins → destruction of fibroblasts,

blood cells, muscle cells → necrosis of muscles, subcutaneous fat with blood vessels thrombosis

- **Postoperative**: after interventions on intestinal system
- **Spontaneous**: due to immune system weakness/intestinal diseases

Food poisoning

- Begins 6–24 hours after ingestion
- Infection of food with spores → food standing temperature 30–50°C/86–122°F → development of vegetative form → **ingestion of infected food** → **toxin production** → ↓ glucose absorption, ↑ water, sodium, chloride secretion → damage of intestinal epithelium

Enteritis necroticans

- Inflammation of jejunum, ileum; type of food poisoning in persons who lack trypsin

RISK FACTORS

- **Gas gangrene**: begins 1–4 days after infection
 - **Traumatic**: **injury** during war/natural disaster; car crash
 - **Postoperative**: GI/biliary surgery; septic abortion
 - **Spontaneous**: colorectal adenocarcinoma; neutropenic states (e.g. AIDS, chemotherapy); intestinal diseases
- **Food poisoning**: improper food-handling
- **Enteritis necroticans**: improper nutrition (e.g. too many sweet potatoes); trypsin inhibitors → ascariasis

COMPLICATIONS

- Disseminated intravascular coagulation; hemodynamic shock, hypotension, renal failure; systemic **hemolysis**; peritonitis; sepsis; death

SIGNS & SYMPTOMS

Gas gangrene

- Two types
 - Cellulitis:** infection of necrotic skin; **crepitation** sounds
 - Clostridial myonecrosis:** infection, destruction of muscles, adjacent tissue
- Paleness, serosanguineous exudate, pain, swelling, tenderness at injury site → color changes to bronze → purple bullae with green/black discoloration due to necrosis
- Characteristic sweet odor
- ↑ heart rate with low-grade fever

Food poisoning

- If only toxins ingested
 - Asymptomatic/diarrhea
- If vegetative form ingested
 - Watery diarrhea without blood/mucus; abdominal cramps, last > 24 hours

Enteritis necroticans

- Abdominal cramps; diarrhea; vomiting; meteorism (excessive gas production in intestines); blood in stool; fever



Figure 56.2 An individual with gas gangrene of the right leg. The causative agent is *Clostridium perfringens*.

DIAGNOSIS

DIAGNOSTIC IMAGING

X-ray

- Gas gangrene:** detection of gas in soft-tissue
- Enteritis necroticans:** small bowel dilatation with presence of gas

LAB RESULTS

- Gas gangrene:** molecular methods for detection of alpha toxins; ELISA, PCR
- Food poisoning:** detection of toxins in feces; PCR

Biopsy

- Gas gangrene:** necrosis of myocytes, connective tissue with small number of neutrophils

OTHER DIAGNOSTICS

- Gas gangrene:** physical examination; characteristic discoloration, odor, crepitation sound

TREATMENT

MEDICATIONS

- Gas gangrene:** antimicrobial therapy (combination of penicillin G, **clindamycin**)
- Enteritis necroticans:** penicillin G/ metronidazole; destruction of bacteria

SURGERY

- Gas gangrene:** removal of dead tissue; hyperbaric oxygen (augments neutrophil, ↓ clostridial exotoxin, spore production); amputation
- Enteritis necroticans:** resection of necrotic intestinal parts

OTHER INTERVENTIONS

- Food poisoning:** oral/IV rehydration

CLOSTRIDIUM TETANI (TETANUS)

osms.it/clostridium-tetani

PATHOLOGY & CAUSES

- Ubiquitously present in soil; resistant to chemical/heat disinfection; terminally present **endospore**; motile
- Anaerobic rod causes nervous system disorder (i.e. tetanus)
- Injury → infection with spores → development of vegetative form in appropriate anaerobic conditions → production of exotoxins (tetanospasmin) → blood/lymphatic transmission → spread to neurons through neuromuscular junction → retrograde transport to spinal cord → endocytosis into inhibitory Renshaw cell interneurons → **exotoxins protease activity cleaves SNARE proteins** → block of **glycine**, gamma-aminobutyric acid (GABA) neurotransmitter-filled vesicles **release** at neuromuscular junction → overactivation of muscles → **muscle spasms**

Virulence factors

- **Two toxins**: tetanolysin (relatively unknown function); **tetanospasmin** (responsible for clinical presentation of tetanus)
- H-antigen from flagelle

Culture

- Oxygen-reduced blood agar with anaerobic incubation

TYPES

- Four types of tetanus
 - **Generalized**: affects whole musculature, from head downwards
 - **Localized**: affects only area near injury
 - **Cephalic**: cranial nerves affected due to head/neck injury
 - **Neonatal**: tetanus occurring in neonates via infection of umbilical stump

RISK FACTORS

- Deep puncture wounds with/without splinters, crush injuries, middle ear infections, frostbites, burns
- IV/subcutaneous drug abuse
- Infected diabetic wounds
- Septic abortion
- Umbilical stump infection via contaminated instruments, hands, cultural practices (e.g. application of cow dung, ghee)
- Lack of vaccination/immunization

COMPLICATIONS

- Cardiac arrest
 - Due to ↑ catecholamine levels, brainstem damage
- Palsies of phrenic, laryngeal nerves due to toxic effect
- Respiratory muscles
 - Apnea
- Vertebral fractures/intramuscular bleeding (due to opisthotonus)

SIGNS & SYMPTOMS

Generalized

- Masseter muscle spasm → trismus/"**lockjaw**" → severe generalized muscle contractions
 - **Risus sardonicus**: characteristic sarcastic-like facial expression due to facial muscles contraction
 - **Opisthotonus**: arched back due to contraction of back muscles
- **Abdominal respiratory muscles, diaphragm**: breathing arrest

Localized

- Weakness, pain of muscles/extremities in proximity of injury
- Stiffness of affected muscles occurring in following days, lasting up to few months
- May progress into generalized form

Cephalic

- Palsy of facial nerve
- Difficulty swallowing
- Weakness of extraocular muscles

Neonatal

- Sucking difficulty in first days of life
- Generalization, opisthotonus may occur

Sympathetic overactivity

- ↑ heart rate, arrhythmias
- Agitation, diaphoresis
- ↑/↓ blood pressure
- Fever
 - Due to overactivity/superinfection



Figure 56.3 This body posture is known as opisthotonus and is caused by the *Clostridium tetani* toxin.

DIAGNOSIS**OTHER DIAGNOSTICS**

- History, physical investigation
- Spatula test
 - Touching oropharynx with spatula causes reflex biting due to masseter spasm

EMG

- Loss/shortening of silent interval between action potentials with continuous discharge from motor units

TREATMENT**MEDICATIONS**

- Human tetanus immunoglobulin (TIG)/intravenous immunoglobulins (IVIG)
 - Neutralization of toxin
- Antibiotics
 - Penicillin, cephalosporins, tetracyclines, metronidazole, vancomycin
- Benzodiazepines
 - Muscle relaxation, sedation
- Muscle relaxants
 - Pancuronium/vecuronium
- Labetalol
 - Autonomic hyperactivity management

OTHER INTERVENTIONS

- Active immunization with tetanus/diphtheria toxoid (Td)
- Respiratory support if needed
- Prevention
 - **Primary:** vaccination at two months of life, with booster doses at 4, 6, 12–18 months, 4–6, 11–12 years (booster doses every ten years later); passive immunization in immunocompromised
 - **Secondary:** vaccination, antitoxin after injury
 - **Tertiary:** vaccination, antitoxin after tetanus presentation

TETANUS MANAGEMENT BASED ON WOUND TYPE, IMMUNIZATION HISTORY

	SMALL WOUNDS		GREATER/DIRTY WOUNDS	
IMMUNIZATION HISTORY	Tetanus/diphtheria toxoid (Td)	Tetanus immune globulin (TIG)	Tetanus/diphtheria toxoid (Td)	Tetanus immune globulin (TIG)
> 3 TETANUS/ DIPHTHERIA TOXOID (Td) DOSES	No	No	No	No
< 3 Td DOSES/ ≥ 10 YEARS FROM LAST BOOSTER/ UNKNOWN	Yes	No	Yes	Yes